

# PUBLISHED VERSION

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**Heart: Cardiac Myxoma**

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## Solid Tumour Section

### Review

## Heart: Cardiac Myxoma

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### Identity

#### Alias

Atrial Myxoma

#### Note

A Cardiac myxoma is a benign gelatinous growth composed of primitive connective tissue cells and stroma resembling mesenchyme that is usually pedunculated and usually arises from the interatrial septum, near the fossa ovalis. The majority (75%) arise within the left atrium. They may be distinguished from thrombi by their endothelial lining and the presence of endothelium-lined crevices and clefts on their surface.

### Classification

#### Note

Cardiac myxomas are typically described by the chamber in which they are located (e.g. atrial myxoma), the side of the heart affected (right vs. left) and their position within a given chamber (posterior wall, anterior wall, interatrial septum or atrial appendage). Thus a cardiac myxoma may be described as a left atrial myxoma of the anterior wall (for example).

### Clinics and pathology

#### Phenotype / cell stem origin

Cardiac Myxomas exhibit a heterogeneous phenotype, with adult cells expressing protein antigens specific to various cell lineages, often within the same tumour, including epithelial, endothelial, myogenic, myofibroblast, neural and neuro-endocrine antigens. Whilst ultrastructural analysis suggests an endothelial derivation, there is considerable dispute as to the outcomes of immunohistochemical investigation. It is believed that cardiac myxomas are derived from a

pluripotent stem cell or a sub-endothelial vasiform reserve cell. The ultrastructural findings suggesting an endothelial origin are supported by recent investigations demonstrating the presence of Nkx2.5/Csx cardiac homeobox gene transcript expression, and the presence of eHAND transcription factors within tumour cells, suggesting a primitive cardiomyocyte phenotype. This argument, however, is weakened by the recent discovery of the presence of Nkx2.5/Csx activation in skeletal myoblasts, and the proliferative effect of Nkx2.5/Csx on neuronal differentiation in vitro. This evidence is supported by the expression of alpha-smooth muscle actin and alpha-cardiac actin in myxomas; indeed, complex myxoma structures (e.g. capillary-like structures) appear to express CD34 on their deeper aspects, with greater alpha-smooth muscle actin expressed on the superficial aspects, suggesting a vessel-like differentiation.

Cardiac Myxomas also show variable response to other antisera, including factor VIII-related antigen, Ulex europaeus agglutinin, vimentin, desmin, myoglobin, S-100 and cytokeratin. Given the variable response to such a broad range of antisera, combined with ultrastructural appearance that commonly suggests an endothelial derivation, but has also been recognised to suggest neural or neuro-endocrine origins, current thought suggests that it is most likely that cardiac myxomas are derived from a pluripotent mesenchymal stem cell or sub-endothelial vasiform reserve cell located around the fossa ovalis and surrounding endocardium. This cell type appears to most commonly follow an endothelial lineage, but is capable of differentiation into other cellular phenotypes. The precise nature of this progenitor cell is not known.

It is important to note that phenotypic expression is variable in these tumours and does not necessarily reflect the tumour origin. It is also important to note the difference between cardiac myxomas and Prichard's structures, which appear to be minute, age-related,

endothelial deformities, and not benign neoplastic growths.

### **Etiology**

Most cardiac myxomas are sporadic and arise as isolated masses in the left atrium. The precise aetiology of cardiac myxomas has proved difficult to delineate, and appears to be related to autosomal dominant gene mutations as described below.

### **Epidemiology**

Cardiac myxomas can occur across all age groups, however, they occur with the greatest frequency amongst between the third and sixth decades of life.

The tumours occur as one of three epidemiological groups of tumour; sporadic cardiac myxomas (by far the most common, with a mean age 56 years old), familial cardiac myxomas and complex cardiac myxomas.

Familial cardiac myxomas usually suggest an autosomal dominant inheritance pattern and exhibit a variable phenotype. Patients with familial cardiac myxomas are generally younger at first diagnosis than those patients presenting with sporadic cardiac myxomas.

Complex cardiac myxomas are a classification of familial tumours, and occur as a syndromic presentation, requiring the presence of a cardiac myxoma with any two or more of the following concurrent conditions;

Skin myxomas

Cutaneous lentiginosis

Myxoid fibromas of the breast

Pituitary adenoma

Primary adrenocortical micronodular dysplasia with Cushing's syndrome

Testicular tumours.

### **Clinics**

#### **Clinical Features:**

#### **Haemodynamic derangement**

Haemodynamic derangement is the most common clinical manifestation of cardiac myxomas, and is due to the ability of the tumour to obstruct pulmonary or venous drainage, or impair flow across the atrio-ventricular valves causing a filling defect. Obstruction of the AV valve orifice occurs more commonly with larger, pedunculated tumours, capable of occluding the valve orifice.

The obstruction due to cardiac myxoma is characteristically progressive and may be associated, as the tumour grows, with intermittent syncope, apparently related to postural change, or sudden cardiac death. These manifestations occur in approximately 25% of patients with left atrial myxomas, 33% of patients with right atrial myxomas and 50% of patients with left ventricular myxomas.

Impairment of valve closure is either due to direct obstruction of the valve orifice by the tumour or damage to the leaflets or chordal apparatus by a

pedunculated tumour capable of 'swinging' into the ventricle during atrial systole (the "wrecking ball" effect). Damage to the leaflets and chordal apparatus leads to regurgitant flow across the valve structure; whilst this occurs in isolation in a minority of patients, it is important to note that obstruction of the valve orifice is the predominant abnormality.

#### **Embolism**

Embolism is a major feature of cardiac myxomas, with systemic embolism occurring in 30-45% of patients with a left atrial tumour. Consequently, the differential diagnosis in cases of peripheral embolism must include cardiac myxoma.

Emboli are typically derived from tumour fragments, detachment of the tumour as a whole, overlying thrombi or foci of infection, and have been reported in every organ system. Emboli may pass to the coronary arteries resulting in occlusion and angina or infarction.

Cerebral emboli characteristically lead to persistent neurological dysfunction, and are reasonably common, with 50% of emboli involving intra- or extra-cranial arteries to the central nervous system.

Large emboli have also been reported as having blocked the abdominal aortic bifurcation.

Left ventricular myxomas have a higher rate of embolism (64%) than those in other locations, and tend to embolise to the brain more frequently than to other sites in the systemic circulation.

Right sided myxomas embolise in approximately 10% of cases, and have the potential to cause fatal pulmonary artery obstruction, although this is rare in comparison to rates of true thromboembolism to the pulmonary arteries in patients with systemic tumour emboli from a left atrial myxoma. It has also been theorised that multiple emboli from a right-sided myxoma may lead to the development of pulmonary hypertension.

#### **Constitutional manifestations**

Constitutional manifestations occur in approximately 30% of cases of cardiac myxoma, and commonly appear as;

- Fatigue
- Fever
- An erythematous rash
- Arthralgia
- Myalgia
- Weight loss, and
- Raynaud's phenomenon.

Polycythaemia with or without associated arterial hypoxia and clubbing associated with right-to-left shunts via an atrial septal defect or patent foramen ovale are unusual, but important manifestations of cardiac myxoma.

Haemolytic anaemia occurs in approximately 33% of cases is due, as is the occasional associated thrombocytopaenia, to mechanical destruction of the formed elements of the blood by abnormal flow across the tumour. Haemolytic anaemia in cardiac myxoma is particularly associated with calcified tumours.

All of the constitutional manifestations of cardiac myxoma are reversible following removal of the tumour.

### Symptoms

- Left Atrial Myxomas

Symptoms associated with left atrial myxomas are primarily due to the haemodynamic derangement caused by the tumour, and very similar in presentation to that of mitral stenosis. Dyspnoea and haemoptysis predominate in the symptomatology and are frequently associated with syncope. The symptoms of left atrial myxoma may rapidly become severe and intractable, and are associated with signs of congestive heart failure.

- Right Atrial Myxomas

Right-sided tumours may present with episodes of syncope and right heart failure, and may progress rapidly despite medical treatment. Common symptoms associated with the failing right heart are prominent jugular a waves, increases in venous pressure, abdominal protuberance due to ascites and hepatomegaly, and peripheral oedema. The absence of orthopnoea and paroxysmal nocturnal dyspnoea in these patients is noteworthy.

Patients may also present with neurological symptoms, Raynaud's phenomenon, angina or dyspnoea secondary to embolisation from the tumour. Similarly, constitutional manifestations may be subtle or absent if the tumour is small, yet in rare cases may be the only evidence of pathology.

### Signs

- Left Atrial Myxomas

Left atrial myxomas may be associated with a loud S1 heart sound produced by prolonged vibrations occurring after mitral valve closure as the tumour momentarily comes to rest in the left atrium. Such mobile tumours, moving between the left ventricle and the left atrium during systole, produce a characteristic notch on the ascending limb of the left ventricular pressure wave due to the sudden increase in left atrial volume as the tumour enters the cavity. Consequently, the loud S1 sound may also be preceded by an ejection sound due to forceful of the tumour from the left ventricle to the left atrium. In cases where the tumour remains in the atrium throughout the cardiac cycle, a diastolic murmur and pressure tracings practically indistinguishable from those of mitral stenosis will likely be present.

The S2 sounds is usually of low intensity and split, and an S3 sound is present as an opening snap or ventricular gallop.

- Right Atrial Myxomas

Right atrial myxomas are associated with a loud, early systolic, widely split S1 due to expression of the tumour from the right ventricle. A pulmonary ejection murmur with a delayed and accentuated pulmonic second sound may be heard. There may also be an early, late or prolonged diastolic murmur heard.

- Ventricular Myxomas

Due to their rarity, the auscultatory findings in ventricular myxomas are not fully known, although may be similar to those of aortic or pulmonary stenosis.

### Laboratory studies

Laboratory studies in cardiac myxoma patients tend to show elevated total globulin levels with pronounced alpha2, beta, and gamma-globulins, localised to the IgM and IgA fractions. These are associated with elevated erythrocyte sedimentation rate and C-reactive protein levels.

Full blood examination may reveal anaemia. Up to 33% of cardiac myxoma patients will suffer haemolytic anaemia due to the mechanical effects of the tumour on the formed elements of the blood.

### Electrocardiography

ECG findings are non-specific in cardiac myxoma, and tend to reflect the haemodynamic derangement secondary to the tumour, frequently indicating atrial enlargement or ventricular hypertrophy. It is not unusual for the patients to be in normal sinus rhythm, and in contrast to mitral valve disease, findings of atrial fibrillation are uncommon. Long-term monitoring may reveal supraventricular arrhythmias associated with atrial tumours and ventricular arrhythmias associated with ventricular tumours.

### Chest Radiography

Radiographic findings are non-specific in cases of cardiac myxoma, generally showing signs of pulmonary hypertension and congestion, with possible cardiomegaly.

### Echocardiography

Two-dimensional echocardiography is the investigational modality of choice in case of cardiac myxoma, allowing the physician to identify the location, size, shape, attachment, and mobility of the tumour, down to diameters of approximately 1-3mm. Transthoracic echocardiography may be supplemented by transoesophageal echocardiography, thus allowing an unimpeded view of the atria, atrial septum and regions of the ventricles. It is also possible for echocardiography to detect cysts, calcifications, necrotic foci and haemorrhage within the tumour.

### CT, MRI and Angiography

CT and MRI imaging modalities are useful in the identification of tumours between 0.5-1cm in diameter, and have the advantage of allowing multiple thoracic slices to be produced without superimposition of the tissues. Similarly, they allow differentiation of different tissue types and may guide the surgeon as to the likely gross morphology of the tumour.

Whilst gated radionuclide cardiac blood-pooling scans can depict a myxoma as an intracavitary filling defect, general angiography has declined in usefulness with regards to the diagnosis of myxomas, and catheterisation of the suspected ventricle is contraindicated due to the risk of tissue embolisation. Angiographic imaging of the coronary arteries however, is useful in patients with

cardiac myxomas (as is indicated in such patients over the age of 40 years old), given the possibility for occlusion from tumour emboli. Coronary angio-graphy can also establish whether or not tumour vessels are supplied from branches of the left or right coronary arteries.

### **Cytology**

Cardiac myxomas characteristically show a pattern of lipid cells embedded in a glycosaminoglycan-rich myxoid stroma. Tumour cells are polygonal and may or may not be multinucleated. They possess eosinophilic cytoplasm and their nuclei typically exhibit an open chromatin pattern. Small areas of cellular atypia may be present, but mitoses are absent. The cells may be spread throughout the stroma, or form clusters around vascular structures, occasionally clustering to form capillary-like structures communicating with the surface of the tumour.

10-20% of cardiac myxomas exhibit calcification and occasional foci of metaplastic bone, and it is not uncommon to find areas of haemorrhage and lymphocyte and macrophage infiltration within the stroma.

The surface of the tumour is composed of polygonal cells with partial coverings of overlying endothelium. The base of the tumour contains many large blood vessels originating from the sub-endocardium.

### **Pathology**

Cardiac myxomas usually appear as grossly round or oval structures with polypoid features, although they may occasionally be gelatinous, and many are prone to spontaneous fragmentation.

The tumours appear white, grey-white, or yellow/brown, and the surface is often covered by thrombi. Tumours can range in size from 1-15cm in diameter, although most measure approximately 5-6cm across.

The mobility of tumours within the heart varies according to the amount of collagen they contain, the degree of attachment to the ventricular wall and the length of the stalk attaching them to the heart.

The precise rate of growth of cardiac myxomas is unknown, although it is believed to be reasonably fast. Whilst essentially non-malignant, there are reported cases of myxoma growth at extra-cardiac sites following embolisation.

### **Treatment**

#### **Indication For Operation**

Operation for resection of a cardiac myxoma is indicated whenever a myxoma is diagnosed. Such operations are generally considered urgent procedures, especially if there is a history of embolism or syncope, as 8-10% of patients awaiting operation die of an embolic complication.

#### **Technique Of Operation**

Surgical resection is the only curative treatment

modality for cardiac myxoma. The standard approach is via median sternotomy under hypo-thermia and cardioplegic cardiac arrest with cardiopulmonary bypass.

The tumour should be removed under direct visualisation and it is vital that fragments are not dislodged during surgery. The surgeon must also ensure that the other atria and ventricles are checked for fragments or other tumour foci.

Complete resection involves the removal of the root of the pedicle attaching the tumour to the heart wall, and consequently a full-thickness removal of the attached inter-atrial septum where appropriate. This in turn creates an atrial septal defect that can be closed primarily with a pericardial or Dacron patch.

In cases where the tumour is associated with the valve structures, it may be necessary to perform a concomitant valve repair, with or without annuloplasty, or, where this is impossible, a valve replacement using an artificial prosthesis.

### **Evolution**

Cardiac myxomas rarely metastasize, although should they do so, their common sites are the brain, sternum, vertebrae, pelvis and scapula. Without treatment, symptomatic patients showing dyspnoea and haemoptysis will likely die within 1-2 years or embolic complications or sudden cardiac death induced by complete valve-orifice occlusion by the tumour.

### **Prognosis**

Long-term outcomes following complete resection of a cardiac myxoma are excellent, with a post-operative mortality rate of 0-3%. Due to their location within the heart, removal of the tumours may result in supra-ventricular arrhythmias or atrio-ventricular node dysfunction requiring treatment.

Cardiac myxomas only recur in 1-3% of cases, and in these instances it can take up to 14 years for recurrence to occur.

## **Cytogenetics**

### **Note**

Chromosomal clonal structural aberrations appear to be the mechanism underlying cardiac myxoma formation, with defects at several foci denoted on chromosomes 2, 12, and 17. Other defects include rearrangements focussed on chromosome 1q32, loss of the Y chromosome and chromosome 13 and 15 telomeric association.

Cytogenetic analysis of myxomas in patients suffering from Carney Complex have shown a role for regions 2p16 and 17q2, however cytogenetic analysis in cases of sporadic myxoma have shown no role for 2p16 and only a limited involvement in structural rearrangement for 17q2. Structural rearrangements in regions 17p1 and 12p1 did occur more frequently, however, and so it has been hypothesized that these regions may contain

genes important in the development of sporadic cardiac myxomas.

## Genes involved and proteins

### Note

Studies have demonstrated that mutations in the PRKAR1a gene encoding the R1a regulatory subunit of cAMP-dependent protein kinase A cause autosomal dominant Carney Complex. This has led to the examination microdissected material from patients with sporadic cardiac myxomas for markers PRKAR1 9CA, D2S2153, D2S2251 and D2S123, however, no loss of heterozygosity was demonstrated, nor were any definite band changes suggestive of microsatellite instability present. This has in turn led to the conclusion that sporadic cardiac myxomas are not genetically related to those found in Carney Complex, and that other, as yet unknown genetic mechanisms must be at work.

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